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(54) Imidazole derivatives as histamine H3-agonists.

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(56) References cited:
US-A- 3 759 944
US-A- 3 891 764
US-A- 3 954 982
TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 10, no. 4, April 1989, pages 159-162; J.F. VAN DER WERF et al.: "The histamine H3 receptor: a general presynaptic histamergic regulatory system?"

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Description

The present invention relates to the use of imidazole derivatives in the manufacture of medicaments having histamine H_3-agonist activity.

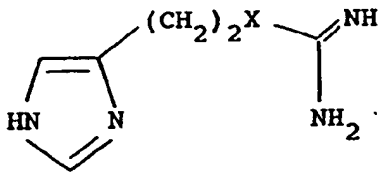
Histamine, a physiologically active compound endogenous in mammals, exerts its action by interacting with certain sites called receptors. One type of receptor is known as a histamine H_1-receptor (Ash and Schild, Brit. J. Pharmac. Chemother. 27 427 (1966)) and the actions of histamine mediated through these receptors are blocked by H_1-antagonists such as mepyramine. A second type of receptor is known as the histamine H_2-receptor (Black et al., Nature 1972, 236, 385) which is not blocked by mepyramine but by H_2-antagonists such as burimamide or cimetidine. A third type of receptor known as the histamine H_3-receptor has more recently been identified (e.g. Arrang et al., Nature 1987, 327 , 117 and Van der Werf et al., (1989) Trends Pharmacol. Sci. 10, 159) which is stimulated by H_3-agonists such as (R)-α-methylhistamine and blocked by H_3-antagonists such as thioperamide.

US-A-3759944 discloses isothiourea derivatives which are described as acting at histamine receptors other than the H_1-receptor and are of utility in inhibiting certain actions of histamine which are not inhibited by H_1-antagonists. A particular isothiourea described is S-[2-(4(5)-imidazolyl)ethyl]isothiourea dihydrobromide or dihydrochloride. This compound is also disclosed in US-A-3954982 wherein it is described as an H_2-antagonist. The prime utility of an H_2-antagonist would be in the treatment of duodenal, gastric, recurrent and stomal ulceration and reflux oesophagitis.

US-A-3891764 discloses amidine derivatives as histamine H_2-antagonists. A particular compound described is 4-(4(5)-imidazolyl)butyramidine dihydrochloride.

It has now been discovered that the above named imidazole compounds are highly potent selective histamine H_3-agonists.

Accordingly the present invention provides the use of a compound of the formula (1):



(1)

or a pharmaceutically acceptable salt thereof:
wherein X is CH_2 or S,
in the manufacture of a medicament having histamine-H_3-agonist activity.

Particular compounds of the formula (1) are:
S-[2-(4(5)-imidazolyl)ethyl]isothiourea or 4-(4(5)-imidazolyl)butyramidine
or pharmaceutically acceptable salts thereof.

These compounds can form pharmaceutically acceptable acid addition salts with hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, citric, maleic, lactic, ascorbic, fumaric, oxalic, methanesulphonic and ethanesulphonic acids.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts can be administered in standard manner for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations can be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions can be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft

gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinylpyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 50 mg, and preferably from 1 mg to 25 mg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 25 mg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.1 mg to 200 mg, preferably 1 mg to 100 mg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.1 mg to 100 mg, for example about 1 mg to 40 mg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required for example from 1 to 4 times a day or by infusion. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are H_1-antagonists such as mepyramine, H_2-antagonists such as cimetidine or ranitidine, phosphodiesterase inhibitors such as theophylline or aminophylline, bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, salbutamol, phenylephrine or ephidrine or anti-allergic agents such as disodium cromoglycate.

The histamine H_3-agonist activity of the compounds of formula (1) was assessed by a method similar to that described by Trzeciakowski (1987), J. Pharmacol. Exp. Ther., 243, 874-880. Inhibition of the electrically evoked twitch responses of the guinea-pig ileum by histamine H_3-receptor agonists was studied by addition of graded concentrations of the compound (in volumes of 25 µl or 79 µl) to the organ bath in a sequential manner. Each concentration of agonist was washed out of the bath when the response had reached equilibrium. A four minute period was allowed between each addition of the compound. The concentration of compound which caused 50% inhibition of the twitch response is given as the EC_{50} (nM). The following results were obtained:

Compound of formula (1)	EC_{50} (nM)
X = S	4.6
X = CH_2	1.1
(R)-α-methylhistamine	6 0

The activity of the compounds of the formula (1) at the histamine H_1- or H_2-receptor was assessed sub-

tantially as described by Parsons et al., Agents and Actions, 1976, 7(1), 31. On the guinea-pig atrium the compound of the formula (1) wherein X is S demonstrated histamine H_2-agonist activity in the range 5 x 10^{-5}M to 10^{-4}M whilst the corresponding compound where X is CH_2 had no histamine H_2-agonist activity up to 10^{-5}M.

Results obtained on the guinea-pig atrium demonstrate weak histamine H_2-antagonist activity :

Compound of formula (1)	pA_2
X = S	4.1
X = CH_2	ca 3.6

On the guinea-pig ileum the compound of the formula (1) wherein X is S demonstrated histamine H_1-agonist activity in the range 10^{-4} to 10^{-3}M, whilst the corresponding compound where X is CH_2 had no histamine H_1-agonist activity up to 10^{-5}M.

On the guinea-pig ileum the compound of the formula (1) wherein X is CH_2 had no histamine H_1-antagonist activity up to 10^{-5}M.

The above results indicate that the compounds of the formula (1) are highly potent selective histamine H_3-agonists, being about 10000 times more potent at the histamine H_3-receptor than at either the histamine H_1- or H_2-receptor.

Agonists of the histamine H_3-receptor are believed to inhibit the synthesis and release of neurotransmitters such as histamine and are therefore likely to decrease neurotransmitter release in the digestive tract and in the nervous, cardiovascular and immune systems. They are likely to have utility as a sedative, as a sleep regulator, anti-convulsant, regulator of hypothalamo-hypophyseal secretion, anti-depressant and modulator of cerebral circulation. Modification of release of the messengers of immune responses is likely to modulate the immune system.

It is believed that the compounds of the formula (1) will be particularly useful in the treatment of allergic diseases such as allergic asthma, allergic rhinitis or urticaria or in the treatment of gastrointestinal motility disorders such as irritable bowel syndrome. The use of histamine H_1- or H_2-antagonists alone or in combination is not regarded as being efficacious. Histamine H_1 or H_2-agonists would be contra-indicated for such disease states.

The following example serves to illustrate a pharmaceutical composition of this invention.

Example 1

A pharmaceutical composition for oral administration is prepared containing:

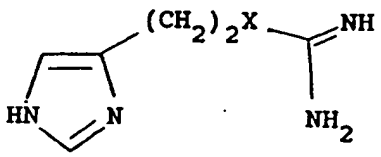
		% by weight
	4-(4-(5)-imidazolyl)butyramidine	55
A	Dibasic calcium phosphate dihydrate	20
	Approved colouring agent	0.5
	Polyvinylpyrrolidone	4.0

		% by weight
	Microcrystalline Cellulose	8.0
	Maize Starch	8.0
B	Sodium glycollate	4.0
	Magnesium Stearate	0.5

by mixing together the ingredients A (substituting lactose or microcrystalline cellose for dibasic calcium phosphate dihydrate if desired), adding a concentrated solution of polyvinylpyrrolidone and granulating, drying and screening the dried granules; adding the ingredients B to the dried granules and compressing the mixture into tablets containing 10 mg, 25 mg or 50 mg of the free base.

Claims

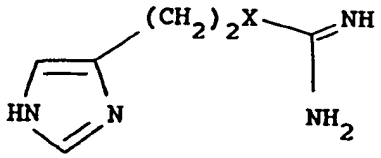
1. The use of a compound of the formula (1):



(1)

or a pharmaceutically acceptable salt thereof wherein X is CH_2 or S in the manufacture of a medicament having histamine H_3-agonist activity.

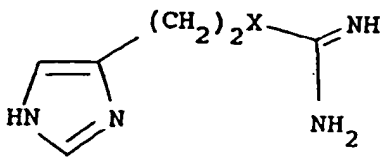
2. The use of a compound of the formula (1):



(1)

or a pharmaceutically acceptable salt thereof wherein X is CH_2 or S in the manufacture of a medicament for treating allergic disease.

3. The use of a compound of the formula (1):



(1)

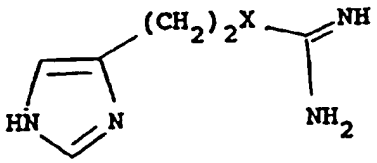
or a pharmaceutically acceptable salt thereof wherein X is CH_2 or S in the manufacture of a medicament for treating gastrointestinal motility disorders.

4. The use according to any one of claims 1 to 3 wherein the compound of the formula (1) is S-[2-(4(5)-imidazolyl)ethyl)isothiourea or a pharmaceutically acceptable salt thereof.

5. The use according to any one of claims 1 to 4 wherein the compound of the formula (1) is 4-(4(5)-imidazolyl)butyramidine or a pharmaceutically acceptable salt thereof.

Patentansprüche

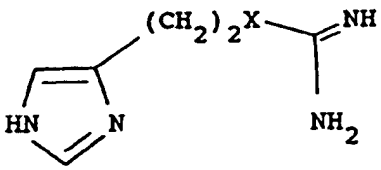
1. Verwendung einer Verbindung der Formel (1)



(1)

oder eines pharmazeutisch verträglichen Salzes davon, wobei der Rest X CH_2 oder S bedeutet, für die Herstellung eines Medikaments mit Histamin H_3-Agonist-Wirksamkeit.

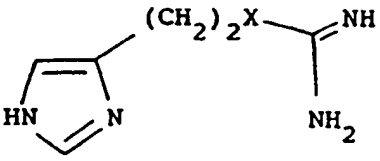
2. Verwendung einer Verbindung der Formel (1)



(1)

oder eines pharmazeutisch verträglichen Salzes davon, wobei der Rest X CH_2 oder S bedeutet, für die Herstellung eines Medikaments zur Behandlung allergischer Erkrankungen.

3. Verwendung einer Verbindung der Formel (1)



(1)

oder eines pharmazeutisch verträglichen Salzes davon, wobei der Rest X CH_2 oder S bedeutet, für die Herstellung eines Medikaments zur Behandlung gastrointestinaler Motilitätsst"rungen.

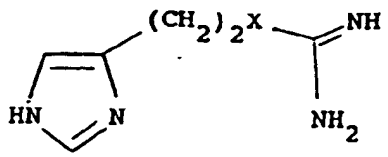
4. Verwendung nach inem der Ansprüche 1 bis 3, wobei die Verbindung der Formel (1) S-[2-(4(5)-Imidaz lyl) thyl]isothioharnstoff oder ein pharmazeutisch verträgliches Salz dav n ist.

5. Verwendung nach in m der Ansprüche 1 bis 4, wobei die Verbindung der Formel (1) 4-(4(5)-

Imidazolyl)butyramidin oder ein pharmazeutisch verträglich s Salz davon ist.

Revendications

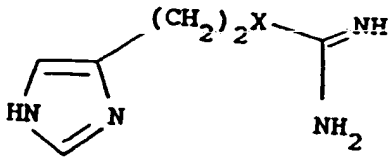
1. Utilisation d'un composé de formule (1):



(1)

ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle X est CH_2 ou S, dans la fabrication d'un médicament ayant une activité agoniste H_3 de l'histamine.

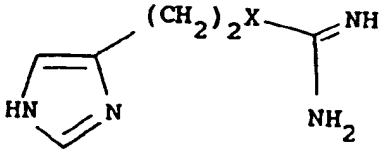
2. Utilisation d'un composé de formule (1):



(1)

ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle X est CH_2 ou S, dans la fabrication d'un médicament pour le traitement de maladies allergiques.

3. Utilisation d'un composé de formule (1):



(1)

ou d'un sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle X est CH_2 ou S, dans la fabrication d'un médicament pour le traitement de troubles de la mobilité gastro-intestinale.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle le composé de formule (1) est la S-[2-(4(5)-imidazolyl)-éthyl]-isothiourée ou un sel de celle-ci acceptable du point de vue pharmaceutique.

5. Utilisation suivant l'une quelconque des revendications 1 à 4, dans laquelle le composé de formule (1) est la 4-(4(5)-imidazolyl)-butyramidine ou un sel de celle-ci acceptable du point de vue pharmaceutique.